PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr PORTRAZZA™

necitumumab

intravenous injection,
800 mg/50 mL (16 mg/mL) in a single dose vial

Antineoplastic

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[Pr] PORTRAZZA™

necitumumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	800 mg/50 mL (16 mg/mL) in a single dose vial	*For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

PORTRAZZA is a recombinant human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 class, which targets the epidermal growth factor receptor (EGFR).

INDICATIONS AND CLINICAL USE

Squamous Non-Small Cell Lung Cancer (NSCLC)
PORTRAZZA (necitumumab) is indicated, in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer who have not received prior chemotherapy for this condition. Patients with locally advanced disease should be considered surgically incurable or incurable by virtue of ineligibility to receive curative surgery.

Geriatrics (≥70 years of age)
In an exploratory analysis, for patients ≥70 years, no apparent benefit toward improved overall survival or progression-free survival was observed. Thus, a thorough assessment should be considered regarding the benefit-risk of adding PORTRAZZA to chemotherapy when making individual treatment decisions (see Special Populations and CLINICAL TRIALS).

Pediatrics (<18 years of age)
The safety and effectiveness of PORTRAZZA in children and adolescents have not been established.

CONTRAINDICATIONS

PORTRAZZA (necitumumab) is contraindicated in patients with previous severe (Grade 3-4) hypersensitivity to necitumumab or to any other ingredient used in the formulation. For a

complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Increased frequency of cardiorespiratory arrest or sudden death (see Cardiovascular, Cardiorespiratory Disorders below)
- Increased risk of venous or arterial thromboembolic events (see Cardiovascular, Thromboembolic Events below)
- Increased risk of electrolyte disorders (magnesium, calcium, potassium, and/or phosphate) (see Monitoring and Laboratory Tests below)

Cardiovascular

Thromboembolic Events

Venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) were observed with PORTRAZZA in combination with gemcitabine and cisplatin (see ADVERSE REACTIONS).

In SQUIRE, the incidence of any grade VTE was 8.2% versus 5.4% (Grade ≥3: 4.3% versus 2.6%) in the PORTRAZZA containing arm compared to the gemcitabine and cisplatin arm. The incidence of any grade ATE was 4.3% versus 3.9% (Grade ≥3: 3.0% versus 2.0%) in the PORTRAZZA containing arm compared to the gemcitabine and cisplatin arm. Administration of PORTRAZZA should be carefully considered in those patients with a history of thromboembolic events (such as pulmonary embolism, deep vein thrombosis, myocardial infarction, and stroke). The relative risk of VTE or ATE was approximately 3-fold higher in patients with a reported history of VTE or ATE than in patients with no reported history of VTE or ATE.

Thromboprophylaxis should be considered after careful assessment of a patient's risk factors (including the increased risk of serious bleeding in patients with tumour cavitation or tumour involvement of large central blood vessels).

Patients and physicians should be aware of signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Discontinuation of PORTRAZZA in patients who experience a VTE or ATE should be considered after a thorough benefit risk assessment for the individual patient.

Cardiorespiratory Disorders
An increased frequency of cardiorespiratory arrest or sudden death was observed with PORTRAZZA. Cardiorespiratory arrest or sudden death was reported in 2.8% (15/538) of patients treated with PORTRAZZA in combination with gemcitabine and cisplatin compared to 0.6% (3/541) of patients treated with gemcitabine and cisplatin alone. Twelve of the fifteen patients died within 30 days of the last dose of PORTRAZZA and had comorbid conditions including history of coronary artery disease (n=3), severe hypomagnesemia (n=4) (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests), chronic obstructive pulmonary disease (n=7), and hypertension (n=5). Eleven of the 12 patients had an unwitnessed death.

Patients with significant coronary artery disease, myocardial infarction within 6 months, uncontrolled hypertension, and uncontrolled congestive heart failure were not enrolled in SQUIRE. The incremental risk of cardiopulmonary arrest or sudden death in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias as compared to those without these comorbid conditions is not known.

Monitoring and Laboratory Tests
In the SQUIRE trial, hypomagnesemia was observed frequently (81.3% when PORTRAZZA was administered with gemcitabine and cisplatin versus 70.2% with gemcitabine and cisplatin alone); this includes Grade ≥3 hypomagnesemia (18.7% versus 7.2%) (see ADVERSE REACTIONS, Table 1). Hypomagnesemia may reoccur at the same grade or worse after a dose delay. Grade ≥3 hypocalcemia (albumin-corrected) was observed in 4.2% of the patients treated on the PORTRAZZA containing arm versus 2.3% of patients treated with gemcitabine and cisplatin alone. When comparing the PORTRAZZA containing arm to the gemcitabine and cisplatin arm, it should be noted that 1.1% versus 0.2% of patients had both Grade ≥3 hypomagnesemia and hypocalcemia (albumin-corrected); furthermore, both Grade ≥3 hypomagnesemia and hypokalemia occurred in 1.7% versus 0.4% of patients. Such concurrent electrolyte abnormalities may increase the risk of potentially serious clinical consequences, although such consequences that could be attributable to such abnormalities were not observed in the SQUIRE trial. In light of these laboratory observations, patients should be carefully monitored for serum electrolytes, including serum magnesium, calcium, potassium and phosphate prior to each PORTRAZZA administration and after completion of PORTRAZZA treatment, until within normal limits. Prompt repletion of electrolytes is recommended, as appropriate.

Sensitivity/Resistance
Hypersensitivity/Infusion-Related Reactions
Hypersensitivity/infusion-related reactions (IRRs) were reported with PORTRAZZA. The onset of events usually occurred after the first or second administration of PORTRAZZA. Monitor patients during and following the infusion for signs of hypersensitivity and infusion-related reactions with resuscitation equipment and appropriate medical resources readily available. In patients who have experienced a previous Grade 1 or 2 hypersensitivity or infusion related reaction to PORTRAZZA, adjust the dose per Table 2 in DOSAGE AND ADMINISTRATION. Immediately and permanently discontinue PORTRAZZA for severe (grade 3 or 4) IRRs.

For management and dose adjustments, see Table 2, DOSAGE AND ADMINISTRATION.

Dermatologic Toxicity

Skin reactions were reported by 77.9% of patients treated with PORTRAZZA in SQUIRE. The skin reactions mainly presented as acneiform rash, dermatitis acneiform, dry skin, pruritus, skin fissures, paronychia and palmar-plantar erythrodysesthesia syndrome. Severe skin reactions were reported in 6.3% of patients. (see Table 1). The onset of events occurred mainly during the first cycle of treatment and resolved within 17 weeks after onset. Immediately and permanently discontinue PORTRAZZA for severe (grade 4) skin reactions (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

For management and dose adjustments, see Table 3, DOSAGE AND ADMINISTRATION.

Eye Disorders

In SQUIRE, eye disorders were more frequently reported in patients treated with PORTRAZZA in combination with gemcitabine and cisplatin compared to patients treated with gemcitabine and cisplatin alone; Grade ≥3 adverse events were reported only in patients treated with PORTRAZZA. Conjunctivitis was the most commonly reported eye disorder; Grade ≥3 conjunctivitis was only reported in two patients during the PORTRAZZA single agent phase. No cases of keratitis were reported.

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening blepharitis, conjunctivitis, or keratitis/ulcerative keratitis with decreased visual acuity should be referred promptly to an ophthalmology specialist.

Warnings and Precautions for Special Populations

Pregnant Women: There are no data from the use of PORTRAZZA in pregnant women. Animal reproduction studies have not been conducted with PORTRAZZA. Based on its mechanism of action and animal models where EGFR expression is disrupted, PORTRAZZA may cause fetal harm or developmental anomalies. PORTRAZZA should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the fetus.

Patients should use effective contraception while receiving PORTRAZZA and for at least 3 months after the last dose of PORTRAZZA (see TOXICOLOGY, Reproductive and Developmental Toxicity).

Fertility in Females and Males of Reproductive Potential: There are no data on the effect of PORTRAZZA on human fertility. Animal studies to assess fertility directly have not been conducted (see TOXICOLOGY).

Nursing Women: It is unknown whether PORTRAZZA is excreted in human milk. Excretion in milk and oral absorption is expected to be low. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with PORTRAZZA and for at least 4 months after the last dose.

Pediatrics (< 18 years): The safety and effectiveness of PORTRAZZA in children and adolescents have not been established.

≥65 years of age: Of the 545 patients in the PORTRAZZA plus gemcitabine and cisplatin arm in SQUIRE, 213 (39.1%) were ≥65 years, including 108 (19.8%) who were ≥70 years. No overall differences in efficacy were reported between patients ≥65 years and <65 years (see CLINICAL TRIALS). There was no evidence of increased incidence of adverse drug reactions in the PORTRAZZA plus gemcitabine and cisplatin arm for patients ≥65 years.

≥70 years of age: Among patients ≥70 years, OS and PFS benefit of PORTRAZZA plus gemcitabine and cisplatin (108 patients [19.8%]) compared to the gemcitabine and cisplatin arm (97 patients [17.7%]) was not demonstrated (see CLINICAL TRIALS). Of the adverse reactions listed in ADVERSE REACTIONS, there was a higher incidence (≥3%) of venous thromboembolic events including pulmonary embolism in patients ≥70 compared to those <70 years. In light of these findings, cardiovascular comorbidities, performance status, and the likely tolerability to chemotherapy with add-on PORTRAZZA should be thoroughly evaluated prior to the initiation of treatment in patients ≥70 years.

PORTRAZZA in Combination with Pemetrexed and Cisplatin
Administration of PORTRAZZA in combination with pemetrexed and cisplatin is not recommended. In a clinical trial in advanced non-squamous NSCLC, patients experienced an increased rate of serious thromboembolic events (including fatal events) in the PORTRAZZA plus pemetrexed and cisplatin arm as compared to the pemetrexed and cisplatin arm (see ADVERSE REACTIONS). The addition of PORTRAZZA did not improve the efficacy outcome over pemetrexed and cisplatin alone in advanced non-squamous NSCLC.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety of PORTRAZZA was evaluated in the SQUIRE study, a global, multicenter, two-arm, randomized, open-label trial comparing PORTRAZZA plus gemcitabine and cisplatin to gemcitabine and cisplatin alone in patients with squamous NSCLC. All patients had ECOG PS 0-2.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Squamous NSCLC – Combination with Gemcitabine and Cisplatin

Patients received PORTRAZZA 800 mg intravenously on days 1 and 8 of each 21 day cycle in combination with up to six cycles of gemcitabine (1250 mg/m^2 on days 1 and 8) and cisplatin (75 mg/m^2 on day 1); hereafter referred to as the chemotherapy phase. Patients in the PORTRAZZA plus gemcitabine and cisplatin arm who demonstrated at least stable disease were permitted to continue to receive additional cycles of PORTRAZZA single agent until disease progression or unacceptable toxicity; hereafter referred to as the PORTRAZZA single agent phase. Patients in the gemcitabine and cisplatin alone arm received a maximum of 6 cycles (chemotherapy phase).

Over the entire PORTRAZZA treatment period (chemotherapy phase and single-agent phase combined), the median duration of exposure to PORTRAZZA in 538 patients who received at least 1 dose of treatment was 4.6 months (range 0.5 months to 34 months), including 182 patients exposed for at least 6 months and 41 patients exposed for greater than 1 year. Patients were monitored for safety until 30 days after treatment discontinuation or resolution of treatment-emergent adverse events.

In SQUIRE (chemotherapy phase), 28.4% of the patients on the PORTRAZZA plus gemcitabine and cisplatin arm discontinued any study drug due to a treatment emergent adverse event compared to 24.6% on the gemcitabine and cisplatin alone arm. The most common TEAEs leading to discontinuation of any study drug, with a rate of ≥1% higher on the PORTRAZZA plus gemcitabine and cisplatin arm, compared to the gemcitabine and cisplatin alone arm were: thrombocytopenia (3.5% versus 1.5%), ATE (2.4% versus 1.3%), anemia (1.9% versus 0.7%), VTE (1.7% versus 0.4%), and skin reactions (1.7% versus 0.2).

For the chemotherapy phase, the most common adverse reactions (all grades) observed in PORTRAZZA-treated patients at a rate of ≥15% and ≥2% higher than gemcitabine and cisplatin alone were skin reactions, vomiting and laboratory abnormalities (hypomagnesemia, albumin-corrected hypocalcemia, hypophosphatemia, and hypokalemia). The most common severe (Grade 3 or higher) adverse events that occurred at a ≥2% higher rate in PORTRAZZA-treated patients compared to patients treated with gemcitabine and cisplatin alone were skin reactions and laboratory abnormalities (hypomagnesemia) (see Table 1).

Table 1: ADRs reported in ≥1% of PORTRAZZA-Treated Patients in SQUIRE (Chemotherapy Phase)

System Organ Class Preferred Term[a]	Number Of Patients (%)			
	PORTRAZZA + GC[b] (N=538)		GC (N=541)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Eye Disorders				
Conjunctivitis[c]	5.6	0	2.2	0
Gastrointestinal Disorders				
Dysphagia	2.2	0.6	2.2	0.2
Mouth ulceration	1.5	0	0.4	0
Stomatitis	10.4	1.1	6.3	0.6

Vomiting	28.8	2.8	25.0	0.9
General Disorders and Administration Site Conditions				
Pyrexia	12.3	1.1	11.1	0.4
Infections and Infestations				
Urinary Tract Infection	4.1	0.2	1.7	0.2
Investigations				
Albumin-Corrected Hypocalcemia[d]	33.0	4.2	22.9	2.3
Hypokalemia[d]	23.6	4.4	17.6	3.2
Hypomagnesemia[d]	81.3	18.7	70.2	7.2
Hypophosphatemia[d]	28.9	6.3	22.7	5.7
Weight Decreased	12.1	0.6	6.3	0.6
Musculoskeletal and Connective Tissue Disorders				
Muscle Spasms	1.7	0	0.6	0
Nervous System Disorders				
Dysgeusia	5.9	0.2	3.3	0
Headache	8.6	0	5.7	0.4
Renal and Urinary Disorders				
Dysuria	2.4	0	0.9	0
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	7.1	0	3.1	0.2
Hemoptysis	8.2	0.9	5.0	0.9
Oropharyngeal pain	1.1	0	0.7	0
Skin and Subcutaneous Tissue Disorders				
Hypersensitivity Reactions/Infusion-Related reactions	1.5	0.4	2.0	0
Skin reactions[e]	77.9	6.3	11.8	0.6
Vascular Disorders				
Arterial Thromboembolic Events[f]	4.3	3.0	3.9	2.0
Venous Thromboembolic Events[g]	8.2	4.3	5.4	2.6
Phlebitis	1.7	0	0.4	0

Abbreviations: GC = gemcitabine and cisplatin alone; PORTRAZZA+GC = necitumumab plus gemcitabine and cisplatin; MedDRA = Medical Dictionary for Regulatory Activities.

[a] MedDRA preferred term (Version 16).

[b] The table reflects the frequency of ADRs during the chemotherapy phase of study treatment in which PORTRAZZA+GC was directly compared with GC.

[c] Conjunctivitis mainly presenting as conjunctivitis, eye irritation, vision blurred, conjunctivitis bacterial, dry eye, and visual acuity reduced.

[d] Based on laboratory assessments. Only patients with baseline and at least one post-baseline result are included.

[e] Skin reactions mainly presenting as acneiform rash, dermatitis acneiform, dry skin, pruritus, skin fissures, paronychia, and palmar-plantar erythrodysesthesia syndrome.

[f] ATE mainly presenting as ischemic stroke, cerebral ischemia, and myocardial infarction.

[g] VTE mainly presenting as pulmonary embolism, deep vein thrombosis, and thrombosis.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

There were no clinically important adverse drug reactions reported in <1% of patients treated with PORTRAZZA in the SQUIRE study.

Description of Selected Adverse Reactions

Thromboembolic events

In SQUIRE (chemotherapy phase), venous thromboembolic events (VTEs) were reported in 8.2% of patients treated with PORTRAZZA in combination with gemcitabine and cisplatin (versus 5.4% in the gemcitabine and cisplatin alone arm) and mainly presented as pulmonary embolism and deep vein thrombosis. Severe VTEs were reported in 4.3% of patients treated with PORTRAZZA in combination with gemcitabine and cisplatin (versus 2.6% in the gemcitabine and cisplatin alone arm). The incidence of fatal VTEs was similar between treatment arms (0.2%). Arterial thromboembolic events (ATEs) were reported in 4.3% of patients treated with PORTRAZZA in combination with gemcitabine and cisplatin (versus 3.9% in the gemcitabine and cisplatin alone arm) and mainly presented as stroke and myocardial infarction. Severe ATEs were reported in 3.0% of patients treated with PORTRAZZA in combination with gemcitabine and cisplatin (versus 2.0% in the gemcitabine and cisplatin alone arm). The incidence of fatal ATEs was 0.6% in the experimental arm versus 0.2% in the control arm (see WARNINGS AND PRECAUTIONS). The relative risk of VTE or ATE was approximately 3-fold higher in patients with a reported history of VTE or ATE than in patients with no reported history of VTE or ATE.

In a clinical trial in advanced non-squamous NSCLC (chemotherapy phase), VTEs were reported in 10.5% of patients treated with PORTRAZZA in combination with pemetrexed and cisplatin (versus 8.3% in the pemetrexed and cisplatin alone arm) and mainly presented as pulmonary embolism and deep vein thrombosis. Severe VTEs were reported in 5.9% of patients treated with PORTRAZZA in combination with pemetrexed and cisplatin (versus 3.5% in the pemetrexed and cisplatin alone arm). ATEs were reported in 3.9% of patients treated with PORTRAZZA in combination with pemetrexed and cisplatin (versus 5.8% in the pemetrexed and cisplatin alone arm) and mainly presented as stroke and myocardial infarction. Severe ATEs were reported in 2.6% of patients treated with PORTRAZZA in combination with pemetrexed and cisplatin (versus 3.5% in the pemetrexed and cisplatin alone arm).

Skin reactions

In the PORTRAZZA plus gemcitabine and cisplatin arm (chemotherapy phase), skin reactions were reported in 77.9% of patients and mainly presented as acneiform rash, dermatitis acneiform, dry skin, pruritus, skin fissures, paronychia and palmar-plantar erythrodysesthesia syndrome. Severe skin reactions were reported in 6.3% of patients. Skin reactions resulted in 1.7% of patients discontinuing any study drug. The majority of skin reactions developed during the first cycle of treatment and resolved within 17 weeks after onset (see WARNINGS AND PRECAUTIONS). In the gemcitabine and cisplatin alone arm, 11.8% reported skin reactions and 0.6% were severe. Skin reactions resulted in 0.2% of patients discontinuing any study drug.

Infusion-related reactions

In the PORTRAZZA plus gemcitabine and cisplatin arm (chemotherapy phase), infusion-related reactions were reported in 1.5% of patients and mainly presented as chills, fever or dyspnea.

Severe infusion-related reactions were reported in 0.4% of patients. The majority of infusion-related reactions developed after the first or second administration of PORTRAZZA. In the gemcitabine and cisplatin alone arm, the IRR and severe IRR rates were 2.0% and 0%, respectively.

Eye Disorders
Eye disorders (MedDRA System Organ Class) occurred approximately 2-fold more frequently in PORTRAZZA plus gemcitabine and cisplatin arm (6.7% in the N + GC arm versus 3.0% in the GC arm). Two patients experienced Grade ≥3 events in the necitumumab arm; both cases occurred during the PORTRAZZA single agent phase. Conjunctivitis (MedDRA Preferred Term) was the most commonly reported adverse event under Eye Disorders (in 3.0% in the N + GC arm versus 0.2% in the GC arm); one case of Grade ≥3 conjunctivitis led to treatment discontinuation.

Monitoring and Laboratory Tests
According to laboratory assessment, the following occurred more frequently in the PORTRAZZA plus gemcitabine and cisplatin arm compared to the gemcitabine and cisplatin alone arm for the chemotherapy phase: hypomagnesemia (any grade, 81.3% versus 70.2%; grade 3 or 4, 18.7% versus 7.2%), albumin-corrected hypocalcemia (any grade, 33.0% versus 22.9%; grade 3 or 4, 4.2% versus 2.3%), hypophosphatemia (any grade, 28.9% versus 22.7%; grade 3 or 4, 6.3% versus 5.7%), hypokalemia (all grade, 23.6% versus 17.6%; grade 3 or 4, 4.4% versus 3.2%) (see Table 1).

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, treatment-emergent anti-necitumumab antibodies (ADA) were detected in 4.0% (34/861) of patients, and neutralizing antibodies were detected in 1.5% (13/861) of patients post exposure to PORTRAZZA. No relationship was found between the presence of ADA and incidence of infusion-related reactions.

DRUG INTERACTIONS

Drug-Drug Interactions
In 12 patients with advanced solid tumors who received gemcitabine and cisplatin in combination with PORTRAZZA, the geometric mean dose-normalized AUC of gemcitabine was increased by 18% and C_{max} increased by 66% compared to administration of gemcitabine alone. The pharmacokinetics of cisplatin were not affected when co-administered with PORTRAZZA. The pharmacokinetics of PORTRAZZA were not affected when co-administered with gemcitabine and cisplatin.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
PORTRAZZA is administered in addition to gemcitabine and cisplatin-based chemotherapy for up to 6 cycles of treatment followed by PORTRAZZA as a single agent in patients whose disease has not progressed, until disease progression or unacceptable toxicity.

The recommended dose of PORTRAZZA is 800 mg (absolute dose) administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3-week cycle. If a decreased infusion rate is indicated, the infusion duration should not exceed 2 hours.

Premedication
In patients who have experienced a previous Grade 1-2 hypersensitivity or infusion-related reaction to PORTRAZZA, premedication with a corticosteroid and an antipyretic in addition to an antihistamine is recommended.

Prior to each PORTRAZZA infusion, premedication for possible skin reactions must be considered.

Dose Adjustments
Recommendations for the management of hypersensitivity/infusion-related and skin reactions are provided in Tables 2 and 3.
Hypersensitivity/Infusion-related reactions

Table 2: Management Recommendations for Hypersensitivity/Infusion-Related Reactions

Toxicity Grade[a]	Management Recommendations (any occurrence)
Grade 1	• Decrease infusion rate by 50% for the duration of infusion.[b] • Monitor patient for worsening of condition.
Grade 2	• Stop the infusion; when the reaction has resolved to Grade ≤1, resume infusion at a 50% decreased infusion rate.[b] • Monitor patient for worsening of condition.
Grade 3-4	• Stop the infusion. • Permanently discontinue treatment with PORTRAZZA

[a] Grade per NCI-CTCAE, Version 3.0
[b] Once the infusion rate has been reduced for a Grade 1 or 2 hypersensitivity/infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

Skin reactions

Table 3: Management Recommendations for Skin Reactions[a]

Toxicity Grade[b]	Management Recommendations (any occurrence)

Grade 3	• Temporarily withhold, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade ≤2.
	• Following improvement to Grade ≤2, re-administer at a dose of 400 mg.
	• This dose may be increased to 600 mg after a minimum of one treatment cycle (3 weeks), if symptoms do not worsen.
	• If symptoms do not worsen for another treatment cycle, the dose may be re-escalated to 800 mg.
	• Permanently discontinue if reactions:
	  • do not resolve to Grade ≤2 after 6 weeks (i.e., after withholding two consecutive doses).
	  • recur or become intolerable at 400 mg.
	• Immediately and permanently discontinue for patients who experience Grade 3 skin induration / fibrosis.

Grade 4	• Immediately and permanently discontinue treatment with PORTRAZZA.

[a] Skin reactions mainly presenting as acneiform rash, dermatitis acneiform, dry skin, pruritus, skin fissures, paronychia and palmar-plantar erythrodysesthesia syndrome.
[b] Grade per NCI-CTCAE, Version 3.0.

Administration

Only use sodium chloride 9 mg/mL (0.9%) solution for injection as a diluent. Do not administer or mix with dextrose solution.

Instructions for Use/Handling

1. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.

2. Each vial is intended for single use only. Inspect the contents of the vials for particulate matter and discoloration. The concentrate for solution for infusion must be clear to slightly opalescent and colorless to slightly yellow prior to dilution. If particulate matter or discoloration is identified, discard the vial.

3. Vials contain 800 mg as a 16 mg/mL solution of PORTRAZZA; one 50 mL vial contains the complete dose. Only use sodium chloride 9 mg/mL (0.9%) solution for injection as a diluent.

To administer using pre-filled intravenous infusion containers

Aseptically remove 50 mL of 0.9% sodium chloride injection, USP from the prefilled 250 mL container and transfer 50 mL of PORTRAZZA medicinal product into the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medicines.

To administer using empty intravenous infusion containers

Aseptically transfer 50 mL of PORTRAZZA medicinal product into an empty intravenous container and add 200 mL of 0.9% sodium chloride, injection, USP to the container to bring the total volume to 250 mL. Gently invert the container to mix. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medicines.

1. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is identified, discard the infusion solution.

2. Discard any unused portion of PORTRAZZA left in a vial, as the product contains no antimicrobial preservatives.

3. Administer over 60 minutes via an infusion pump. A separate infusion line must be used and the line must be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection at the end of the infusion.

OVERDOSAGE

There has been limited experience with PORTRAZZA overdose in human clinical trials. The highest dose of PORTRAZZA studied clinically in a human dose-escalation Phase 1 study is 1,000 mg once a week or once every other week. Two out of 9 patients in the every other week cohort experienced dose-limiting adverse events including Grade 3 headache, vomiting, and nausea. There is no known antidote for PORTRAZZA overdose.

For management of a suspected drug overdose, contact your regional Poison Control Center.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Necitumumab is a recombinant human IgG1 monoclonal antibody that binds with high affinity and specificity to the human epidermal growth factor receptor 1 (EGFR) and blocks the ligand binding site, blocking activation by all known ligands and inhibiting relevant biological effects *in vitro*. Studies demonstrate that PORTRAZZA inhibits EGFR-dependent tumor cell proliferation, and can exert cytotoxic effect in tumor cells through antibody-dependent cell-mediated cytotoxicity.

Pharmacodynamics

Activation of EGFR has been correlated with malignant progression, inhibition of tumor cell death (apoptosis) and induction of angiogenesis. In addition, PORTRAZZA induces EGFR internalization and degradation *in vitro*. Studies in cell line-derived xenograft models of human cancer, including non-small cell lung carcinoma, demonstrate that PORTRAZZA has antitumor activity both in monotherapy and in combination with gemcitabine and cisplatin.

A study on the impact of necitumumab treatment on the QT/QTc interval in heavily pre-treated patients with advanced solid tumors treated with necitumumab 800 mg once a week over a 6-week cycle, demonstrated lack of effect on QTc interval (per ICH E14 guidelines). However, treatment-emergent adverse events of QTc prolongation were reported in one third of patients. QTc prolongation may be caused by electrolyte disturbances. Electrolyte disturbances are a known side effect of cytotoxic drugs and EGFR mAbs.

Pharmacokinetics

PORTRAZZA is a large protein drug, which is administered through intravenous infusion. Following the dose regimen of 800 mg PORTRAZZA on day 1 and day 8 of a 21 day schedule, the geometric mean of PORTRAZZA C_{min} was 98.5 µg/mL (Coefficient of Variation 80%) in serum from patients with squamous NSCLC after five cycles of treatment in combination with gemcitabine and cisplatin. A population pharmacokinetic model used to analyse the pharmacokinetics of PORTRAZZA reflects that inter-patient variability was moderate to high for primary parameters (see Table 4).

Table 4: Summary of PORTRAZZA Pharmacokinetic Parameters Obtained From Population Analysis of Data in Cancer Patients

Parameter Description	Population Estimate (%RSE)	Inter-Patient Variability (%RSE)	η shrinkage
Clearance[a] (CL_{tot})		28.8% (10.5)	10.3%
CL (L/h)	0.0114 (4.0)		
K_m (µg/mL)	7.97 (24.1)		
V_{max} (mg/h)	0.565 (13.2)		
Central Volume of Distribution, V_1 (L)[b]	3.41 (2.9)	21.1% (18.8)	44.7%
Inter-compartmental Clearance, Q (L/h)	0.0183 (8.3)		
Peripheral Volume of Distribution, V_2 (L)[b]	3.29 (4.1)	55.4% (20.7)	46.0%
Weight-CL[c] and Q[d]	0.768 (8.7)		
Weight-V_1[e] and V_2[f]	0.498 (15.7)		
Inter-Patient Variability Correlation Coefficient (CL_{tot} and V_1)	0.609 (19.4)		
Residual Error			
Additive (µg/mL)	10.8 (11.5)		
Proportional	23.7% (3.4)		

Abbreviations: RSE= relative standard error.

[a] Total clearance (CL_{tot}) is the sum of linear and nonlinear clearances. $CL_{tot}=CL + V_{max}/(C+K_m)$

[b] Volume at steady state (V_{ss}) is the sum of central and peripheral volumes of distribution. $V_{ss}=V_1+V_2$

[c] $C_{ind} = CL * (bodyweight/70)^{0.768}$

[d] $Q_{ind} = Q * (bodyweight/70)^{0.768}$

[e] $V_{1,ind} = V_1 * (bodyweight/70)^{0.498}$

[f] $V_{2,ind} = V_2 * (bodyweight/70)^{0.498}$

Absorption: PORTRAZZA is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution: After an initial peak, the concentration with time of PORTRAZZA can be approximated with a biphasic decline. Based on a noncompartmental analysis, the parameter for the combined conceptual volume of distribution at steady state (Vss) for necitumumab was estimated to be 3.92 L. The observed maximum serum concentration (C_{max}) after the first 800 mg dose of PORTRAZZA was 288 µg/mL).

Elimination: Necitumumab exhibits concentration-dependent clearance, through target mediated drug distribution. The current PopPK model for necitumumab predicted that the time to reach steady state was approximately 100 days and that the serum drug concentrations produced from 800 mg PORTRAZZA on day 1 and day 8 of a 21-day schedule would be greater than the EC_{50} of 82 µg/mL and thus sufficient for therapeutic efficacy.

Changes in PK Variables in the Presence of Anti-drug Antibodies:
In the SQUIRE study, the PopPK model estimated the parameter CL_{tot} of necitumumab to be 27% higher and the parameter $C_{ss,ave}$ to be 34% lower in patients who tested positive for ADA post-treatment than patients who tested negative for ADA post-treatment.

Special Populations and Conditions

Population pharmacokinetic analysis could not detect any effect of age, gender, race, liver status, and kidney function on the pharmacokinetics of PORTRAZZA, while CL and volume of distribution had a less than proportional positive correlation with body weight. Although modeling results suggest that the disposition of PORTRAZZA was statistically dependent on body weight, simulations indicated that weight-based dosing would not significantly decrease PK variability.

Geriatrics: A population pharmacokinetic analysis could not detect an impact of age on PORTRAZZA exposure.

Hepatic Insufficiency: No formal studies have been conducted to evaluate the effect of hepatic impairment on the PK of PORTRAZZA.

Renal Insufficiency: No formal studies have been conducted to evaluate the effect of renal impairment on the PK of PORTRAZZA.

STORAGE AND STABILITY

Vials: Store in a refrigerator (2°C – 8°C). Do not freeze or shake. Keep the vial in the outer carton in order to protect from light.

Infusion Solution: After dilution and preparation, the medicine should be used immediately. The chemical and physical stability for the necitumumab infusion solution was demonstrated for up to 24 hours at 2° to 8°C, or for 4 hours at up to 30°C. DO NOT FREEZE OR SHAKE the infusion solution. Do not administer the solution if you notice any particulate matter or discoloration. The color of the solution may vary from a slightly opalescent and colorless to slightly yellow without visible particles.

Dosage Forms, Composition and Packaging

PORTRAZZA is supplied in a 50 mL single-dose vial as a sterile, preservative-free solution for intravenous infusion. Vials are individually packaged in a carton. Each vial contains 800 mg necitumumab in 50 mL (16 mg/mL). Non-medicinal ingredients are: citric acid anhydrous, glycine, mannitol, polysorbate 80, sodium chloride, sodium citrate dihydrate and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Necitumumab

Chemical name: Immunoglobulin G1, anti-(human epidermal growth factor receptor) (human monoclonal IMC-11F8 γ1-chain), disulfide with human monoclonal IMC-11F8 κ-chain, dimer

Immunoglobulin G1, anti-(human endothelial growth factor receptor (receptor tyrosine-protein kinase ErbB1, EC 2.7.10.1)); human monoclonal IMC-11F8 γ1 heavy chain (224-214')-disulfide with human monoclonal IMC-11F8 κ light chain dimer (230-230":233-233")-bisdisulfide

Structure: PORTRAZZA (necitumumab) is an anti-EGFR recombinant human monoclonal antibody of the IgG1 class, designed to block the ligand binding site of the human EGFR. It is composed of four polypeptide chains, two identical gamma (γ) heavy chains consisting of 451 amino acids each, and two identical kappa light chains consisting of 214 amino acids each. The antibody contains one conserved N-linked glycosylation site at each heavy chain, in the Fc region.

Molecular mass: PORTRAZZA has an approximate molecular weight of 144.8 kDa.

Physicochemical properties: Clear to slightly opalescent and colorless to slightly yellow liquid. The solution pH is 5.7-6.3. The osmolality is 250 to 320 mOsm/kg.

Product Characteristics

Necitumumab is produced in genetically engineered mammalian NS0 cells.

Necitumumab drug product is a sterile, preservative-free solution for infusion of necitumumab formulated in an aqueous solution at a concentration of 16 mg/mL.

All excipients used for the manufacture of necitumumab drug product are of pharmacopeial grade.

The excipients used in the necitumumab drug product are not of human or animal origin.

CLINICAL TRIALS

Study Demographics and Trial Design

Table 5: Study Demographics and Trial Design - SQUIRE

Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Median age years (range)	Gender (%)
Global, multicenter, two-arm, randomized open label study	PORTRAZZA+GC PORTRAZZA at 800 mg (days 1 and 8) plus chemotherapy consisting of gemcitabine at 1,250 mg/m^2 (days 1 and 8) and cisplatin at 75 mg/m^2 (day 1); every 3 weeks GC Alone Gemcitabine-cisplatin chemotherapy alone consisting of gemcitabine at 1,250 mg/m^2 (days 1 and 8) and cisplatin at 75 mg/m^2 (day 1); every 3 weeks	PORTRAZZA+GC n = 545 GC Alone n = 548	PORTRAZZA+GC 62 (32-84) GC Alone 62 (32-86)	PORTRAZZA+GC Male - 450 (83%) Female – 95 (17%) GC Alone Male - 458 (84%) Female – 90 (16%)

SQUIRE, a global, multicenter open-label, two-arm, randomized study of PORTRAZZA, was conducted in 1,093 patients with stage IV (American Joint Committee on Cancer Version 7) squamous NSCLC, including patients with ECOG PS2, who had received no prior anticancer therapy for metastatic disease (see Table 5). Patients were randomized to receive PORTRAZZA at 800 mg plus chemotherapy consisting of gemcitabine at 1,250 mg/m^2 and cisplatin at 75 mg/m^2 (PORTRAZZA plus gemcitabine and cisplatin Arm), or gemcitabine-cisplatin chemotherapy alone. Stratification factors were ECOG performance status (0, 1 versus 2) and geographic region (North America, Europe, and Australia versus South America, South Africa, and India versus Eastern Asia). PORTRAZZA and gemcitabine were administered on days 1 and 8 of each 3-week treatment cycle, and cisplatin was administered on day 1 of each 3-week treatment cycle. There was no premedication for PORTRAZZA mandated by the study. Pre-emptive treatment for skin reaction was not permitted prior to the beginning of the second treatment cycle. Patients received a maximum of six cycles of chemotherapy in each arm; patients in the PORTRAZZA plus gemcitabine and cisplatin arm who had no progression continued to receive single-agent PORTRAZZA until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival (OS) and the main secondary efficacy endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Patients underwent radiographic assessment of disease status every six weeks, until radiographic documentation of progressive disease (PD).

Study Results

Demographics and baseline characteristics were balanced between arms (see Table 6). In the

PORTRAZZA plus gemcitabine and cisplatin arm, 51% of patients continued with single-agent PORTRAZZA after completing chemotherapy. Use of post-study systemic therapy was similar in the 2 arms (47.3% in the PORTRAZZA plus gemcitabine and cisplatin arm and 44.7% in the gemcitabine and cisplatin alone arm).

Table 6: SQUIRE Demographics and Disease Characteristics (ITT Population)

Characteristic	GC+N N = 545 n (%)	GC N = 548 n (%)	Total N = 1093 n (%)
Age (years)			
Median	62.0	62.0	62.0
Range`	32 – 84	32 - 86	32 - 86
Age Group, n (%)			
<65 years	332 (60.9)	340 (62.0)	672 (61.5)
≥65 years	213 (39.1)	208 (38.0)	421 (38.5)
<70 years	437 (80.2)	451 (82.3)	888 (81.2)
≥70 years	108 (19.8)	97 (17.7)	205 (18.8)
Sex, n (%)			
Male	450 (82.6)	458 (83.6)	908 (83.1)
Female	95 (17.4)	90 (16.4)	185 (16.9)
ECOG PS at baseline, n (%)			
0	164 (30.1)	180 (32.8)	344 (31.5)
1	332 (60.9)	320 (58.4)	652 (59.7)
2	49 (9.0)	47 (8.6)[a]	96 (8.8)[a]
Race, n (%)			
White	457 (83.9)	456 (83.2)	913 (83.5)
Asian	43 (7.9)	42 (7.7)	85 (7.8)
Black or African American	5 (0.9)	6 (1.1)	11 (1.0)
All Others	40 (7.3)	44 (8.0)	84 (7.7)
Smoking History			
Ex-Light Smoker	18 (3.3)	26 (4.7)	44 (4.0)
Non-Smoker	26 (4.8)	27 (4.9)	53 (4.8)
Smoker	500 (91.7)	495 (90.3)	995 (91.0)
Missing	1 (0.2)	0	1 (0.1)
Geographic Region			
North America, Europe, Australia	472 (86.6)	475 (86.7)	947 (86.6)
South America, South Africa, India	30 (5.5)	32 (5.8)	62 (5.7)
Eastern Asia	43 (7.9)	41 (7.5)	84 (7.7)
Disease Stage at Study Entry[b], n (%)			
IIIB without malignant pleural effusion (AJCC 6)	1 (0.2)	1 (0.2)	2 (0.2)
IV[c]	543 (99.6)	546 (99.6)	1089 (99.6)
Missing	1 (0.2)	1 (0.2)	2 (0.2)
Number of Metastatic Organ Systems, n (%)			
1 organ system	51 (9.4)	50 (9.1)	101 (9.2)
2 organ systems	193 (35.4)	193 (35.2)	386 (35.3)
>2 organ systems	301 (55.2)	304 (55.5)	605 (55.3)
Disease Histology, n (%)			
Squamous	543 (99.6)	545 (99.5)	1088 (99.5)
Other Histology[d]	2 (0.4)	3 (0.5)	5 (0.5)

Abbreviations: AJCC = American Joint Committee on Cancer Staging Manual; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; GC = gemcitabine and cisplatin; GC+N = gemcitabine plus

cisplatin plus necitumumab; ITT = intent to treat; N = number of randomized patients; n = number of patients in category; NSCLC = non-small cell lung cancer; PS = performance status.

[a] One patient with ECOG PS = 3 at baseline was randomized to the GC Arm; this patient did not receive treatment.

[b] Per AJCC Staging Manual, edition effective at the time of randomization (Sixth or Seventh Edition).

[c] Includes patients with Stage IIIb disease with malignant pleural effusion, defined as Stage IV under AJCC7.

[d] No confirmation of squamous NSCLC (considered as major protocol deviation).

The SQUIRE study met its primary endpoint by demonstrating a statistically significant improvement in OS in the PORTRAZZA plus gemcitabine and cisplatin arm versus the gemcitabine and cisplatin alone arm, with a 16% reduction in the risk of death (HR = 0.842; p=.0120). The OS data were supported by a statistically significant improvement in PFS (HR = 0.851; p=.0201), with a risk reduction for progression or death of 15% in the necitumumab arm (see Table 7 and Figure 3).

There was no statistical difference in ORR between arms, with an ORR of 31% (95% CI 27, 35) for PORTRAZZA plus gemcitabine and cisplatin arm and an ORR of 29% (95% CI 25, 33) for gemcitabine and cisplatin alone arm, p-value = 0.40. The DCR (CR+PR+SD) was 81.8% (78.4, 84.8) for the PORTRAZZA plus gemcitabine and cisplatin Arm compared with 77.0% (73.3, 80.3) for the GC Arm.

Table7: Summary of Efficacy Data (ITT population) – SQUIRE

	PORTRAZZA+GC Arm N=545	**GC Arm N=548**
Overall survival		
Number of events (n)	418	442
Median – months (95% CI[a])	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Hazard ratio (95% CI)[b, c]	0.84 (0.74, 0.96)	
Two-sided log-rank p-value[c]	0.012	
1-year Overall survival rate (%)	47.7	42.8
2-year Overall survival rate (%)	19.9	16.5
Progression free survival		
Number of events (n)	431	417
Median – months (95% CI)	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Hazard ratio (95% CI) [b, c]	0.85 (0.74, 0.98)	
Two-sided log-rank p-value[c, d]	0.020	

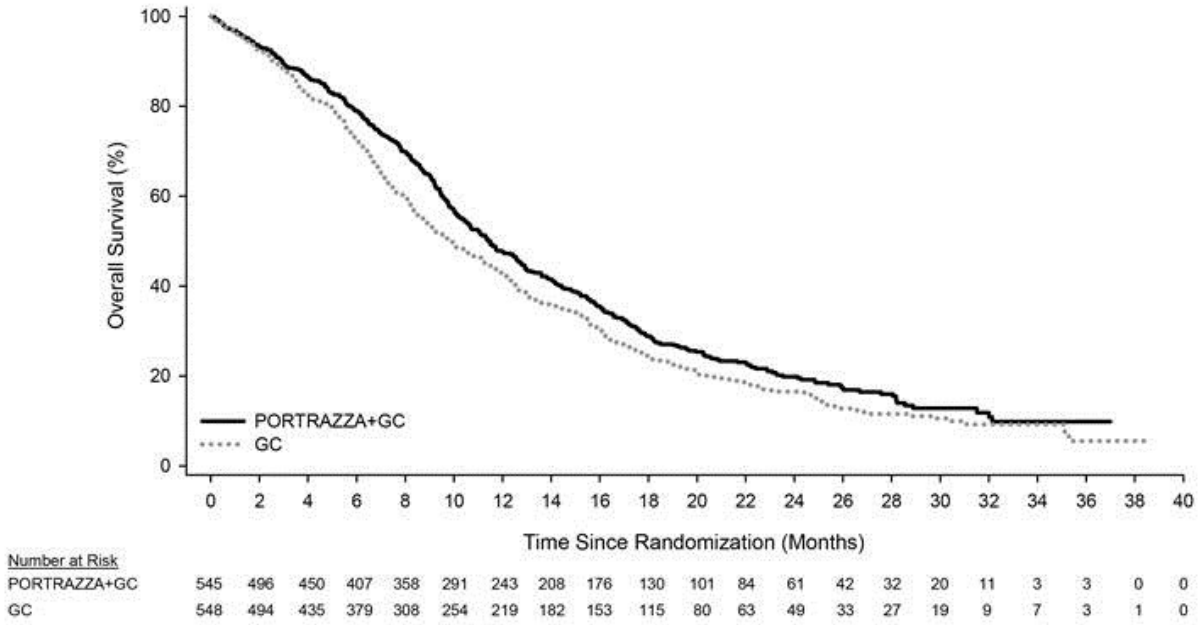
[a] Abbreviations: CI = confidence interval.

[b] Hazard ratio is expressed as treatment/control and estimated from Cox model.

[c] Stratified by the randomization strata (ECOG PS [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

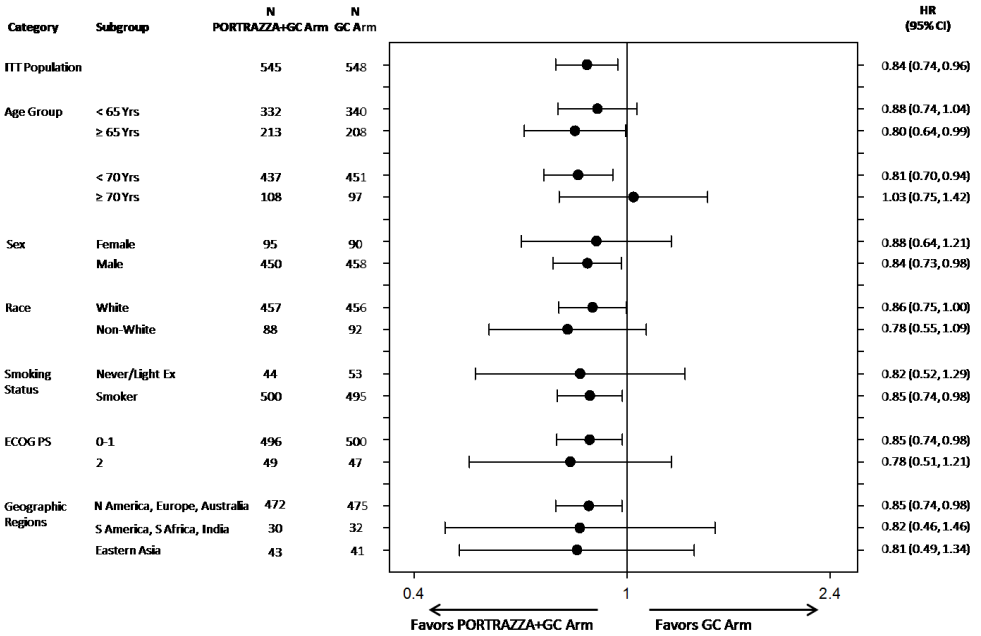
[d] Hochberg's method was used to adjust for multiplicity testing for the secondary endpoints.

Figure 1. Kaplan-Meier curve for overall survival in the ITT population



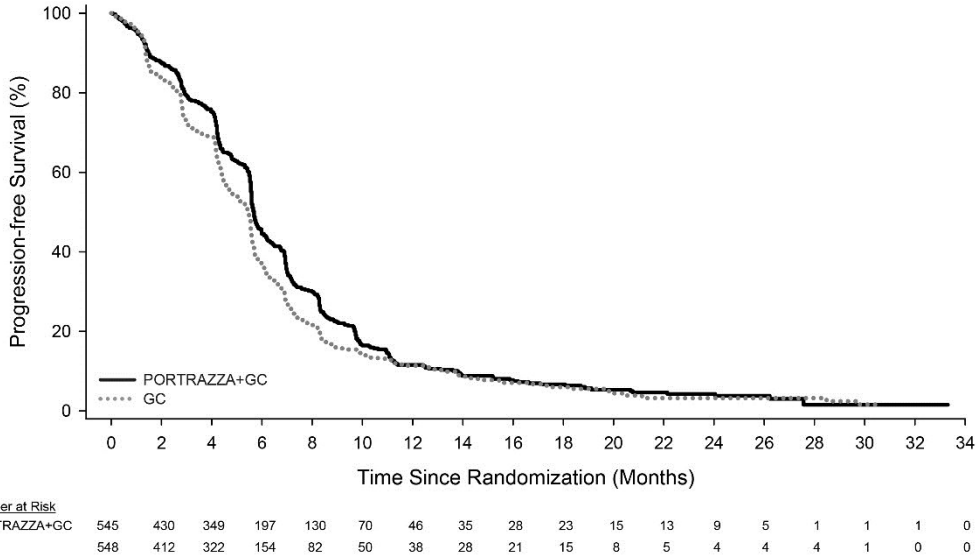
An improvement was observed in all but one of the pre-specified subgroups for OS, including those defined by stratification factors (ECOG PS score [0-1 versus 2] and geographic region [North America, Europe, and Australia versus South America, South Africa, and India versus Eastern Asia]). No improvement in OS was seen for patients ≥70, for whom the hazard ratio for overall survival was 1.03 (0.75, 1.42) (see Figure 2).

Figure 2. Forest plot for subgroup analysis of overall survival (ITT population)



Abbreviations: C = cisplatin; G = gemcitabine; ITT = intent-to-treat.

Figure 3. Kaplan-Meier curve for PFS in the ITT population



DETAILED PHARMACOLOGY

Nonclinical Pharmacodynamics

In vitro

Nonclinical pharmacodynamic studies of necitumumab in vitro demonstrate EGFR selectivity, high affinity binding to human (Kd = 0.320 nM) and cynomolgus monkey EGFR, and ability to potently inhibit ligand binding to EGFR (IC50 < 0.700 nM). The results of *in vitro* functional studies indicate that necitumumab inhibits ligand-induced EGFR phosphorylation, whereby receptor activation and downstream signaling effectors such as Erk1/2 are inhibited, modestly promotes EGFR internalization and degradation and is capable of eliciting immune effector mechanisms such as ADCC.

In vivo

Nonclinical studies in xenograft tumor models indicate that treatment with necitumumab results in tumor growth inhibition in the setting of NSCLC (lung adenocarcinoma and squamous carcinoma of the lung), CRC and other tumor types. Necitumumab exhibits antitumor activity *in vivo* as single agent and in combination with gemcitabine and cisplatin, paclitaxel and cisplatin (NSCLC), irinotecan or oxaliplatin (CRC) in a subset of lung and colon xenograft tumor models. Inhibition of tumor cell proliferation and/or survival appears to be a mechanism of action of this antibody. Results of pharmacokinetic/pharmacodynamic (PK/PD) study in xenograft BxPC-3 model in which necitumumab was administered by the ip route showed that tumor growth was inhibited at doses ranging from 6 to 60 mg/kg, with 50% tumor growth inhibition occurring when plasma antibody concentration was maintained above 60 µg/mL.

Nonclinical Pharmacokinetics
The pharmacokinetic profile of necitumumab is consistent with that expected for a monoclonal antibody in both mice and monkeys. In mice, the half-life was approximately 4.8 days after both intravenous and intraperitoneal administrations. The half-life in monkeys after intravenous administration ranged from 3.1 days to 4.8 days resulting in accumulation after 26-weeks of dosing that ranged from 1.1 to 1.7-fold based on C_{max}. Systemic exposure to necitumumab increased with increasing dose in both mice and monkeys. After repeat dosing in monkeys, dose-dependent changes in clearance and half-life resulted in a greater than proportional increase in exposure following intravenous administration. No consistent sex-related differences in exposure were observed in monkeys. Steady-state volume of distribution was approximately equal to the vascular space in monkeys suggesting that distribution of necitumumab was limited to the vasculature. Necitumumab, similar to other antibodies, is expected to be eliminated via catabolism to small peptides and amino acids.

TOXICOLOGY
The nonclinical testing strategy for necitumumab was designed to demonstrate the potential efficacy of necitumumab and to support its chronic administration to patients with advanced cancer. Completed animal studies with necitumumab to assess the safety of necitumumab include 5-week and 26-week repeat-dose toxicology studies with toxicokinetic evaluation in monkeys. These Good Laboratory Practices (GLP)-compliant nonclinical studies were conducted in the cynomolgus monkey, which was established as an appropriate species for toxicity testing based on similar tissue cross-reactivity patterns and similar EGFR binding affinity in humans and monkeys

Single-Dose Toxicity
No dedicated single-dose toxicity studies were conducted with necitumumab. However, no unexpected toxicities were observed in monkeys exposed to high systemic concentrations of necitumumab (doses up to 60 mg/kg) during the 26-week, repeat-dose monkey study.

Repeat-Dose Toxicity
GLP-compliant 5-week and 26-week, repeat-dose toxicity studies of necitumumab given once weekly by intravenous infusion to cynomolgus monkeys were conducted to support clinical trials and the chronic administration of necitumumab to oncology patients.
The high doses for each of the toxicity studies were chosen to generate animal exposure that substantially exceeded the anticipated clinical dose and exposure. Standard toxicological, local tolerance and toxicokinetic parameters were monitored in both studies. Effects on major organ systems were evaluated as part of these repeat-dose studies.

A no-observed-adverse-effect level (NOAEL) was not established in the 26-week repeat-dose study in monkeys, as skin toxicity was observed at all dose levels, with dose dependent severity and time of onset. Skin effects were described as hyperplastic dermatitis which presented as rash, erythema, and scaling macroscopically and epidermal hyperplasia, hyperkeratosis and lymphocytic interface inflammation microscopically. This type of skin lesion is characteristic of many EGFR-inhibitors.. Once skin lesions were observed (starting in week 5), animals were given palliative treatment, including antibiotic ointment. One animal died due to septicemia, that

was possibly related to skin lesions. No unexpected toxicities were identified in monkeys exposed to high systemic concentrations of necitumumab.

Exposure levels in the 5-week repeat-dose monkey study were similar to the median clinically efficacious exposure level, while exposure in the 26-week monkey study exceeded the clinically efficacious exposure level by approximately 2-fold. Overall, the toxicology data suggest that patients can be exposed to therapeutically effective necitumumab concentrations while only experiencing monitorable and clinically manageable skin effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Specific animal studies to test necitumumab for carcinogenic potential or potential to impair fertility have not been performed. The risk of fertility impairment is unknown. However, no adverse effects on male or female reproductive organs were observed in monkeys treated during the 26-week, repeat-dose monkey study.

Reproductive and Developmental Toxicity
Human IgG1 is known to cross the placenta; therefore, necitumumab has the potential to be transmitted from the mother to the developing fetus. No animal studies have been specifically conducted to evaluate the effect of necitumumab on reproduction and fetal development . Epidermal growth factor receptor (EGFR) is involved in very early to late gestational development processes and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Disruption or depletion of EGFR expression in animal models resulted in fetal harm or developmental anomalies including effects on placental, lung, cardiac, skin, and neural development. In mice, the disruption of the EGF/EGFR signaling pathway resulted in embryo-fetal lethality, teratogenicity, and post-natal death.

Local Tolerance
Local tolerance was investigated during the 26-week, repeat-dose monkey study. Dose dependent reversible skin toxicity was observed. The skin effects were consistent with the known class effects of EGFR inhibitors.

REFERENCES

1. Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, Ramlau R, Galiulin RK, Bálint B, Losonczy G, Kazarnowicz A, Park K, Schumann C, Reck M, Depenbrock H, Nanda S, Kruljac-Letunic A, Kurek R, Paz-Ares L, Socinski MA; SQUIRE Investigators. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as firstline therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomized, controlled phase 3 trial. *Lancet Oncol.* 2015;16(7):763-774.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PORTRAZZA
necitumumab

Read this carefully before you receive PORTRAZZA (pronounced "por-traz-za"). This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about PORTRAZZA.

Serious Warnings and Precautions

- **Increased frequency of heart attack or sudden death**
- **Increased risk for blood clots in your veins or arteries**
- **Increased risk of low blood levels of magnesium, calcium, potassium, or phosphate**

What is PORTRAZZA used for?

- PORTRAZZA is a cancer medicine used in combination with gemcitabine and cisplatin (other anti-cancer medicines) for the treatment of patients with a type of advanced lung cancer (called squamous non-small cell lung cancer) who have not received prior chemotherapy for this condition.

How does PORTRAZZA work?

- PORTRAZZA contains the active substance necitumumab, which belongs to a group of biologic substances called monoclonal antibodies.
- PORTRAZZA recognizes and binds specifically to a protein on the surface of some cancer cells. The protein is known as an epidermal growth factor receptor (EGFR). Other body proteins (called growth factors) can attach to the EGFR and stimulate the cancer cell to grow and divide. PORTRAZZA stops other proteins from binding to the EGFR and thus prevents the cancer cell from growing and multiplying.

What are the ingredients in PORTRAZZA?

- Medicinal ingredients: necitumumab
- Non-medicinal ingredients: citric acid anhydrous, glycine, mannitol, polysorbate 80, sodium chloride, sodium citrate dihydrate and water for injection

PORTRAZZA comes in the following dosage forms:

- PORTRAZZA is available as a solution in 50 mL single use vials. Each vial contains 800 mg/50 mL (16 mg/mL).
- After dilution and preparation, PORTRAZZA is administered as an intravenous (I.V.) infusion.

Do not use PORTRAZZA if:

- you are allergic to this drug or to any ingredient in the formulation.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PORTRAZZA. Talk about any health conditions or problems you may have, including if you:

- have had blood clots in the veins or the arteries ('venous thromboembolic events and arterial thromboembolic events');
- have ever had a heart attack or stroke;
- have ever had low blood levels of magnesium, calcium, potassium or phosphate;
- have ever had an allergic reaction to an infusion;
- have ever had skin reactions after treatment with a drug;
- are pregnant or plan to become pregnant;
- are breastfeeding;
- have any allergies to this drug or to its ingredients.

Other warnings you should know about:

- Avoid getting pregnant while receiving this medicine and for at least 3 months after the last dose of PORTRAZZA as this medicine may potentially cause harm to your unborn child. Talk to your doctor about the best contraception for you.
- Do not breast-feed your baby during treatment with PORTRAZZA and for at least 4 months after you receive the last dose, as this medicine may harm the growth and development of your baby.

Elderly Patients (70 years and older):

- Talk with your healthcare professional about the individual benefits and risks of adding PORTRAZZA to chemotherapy, as no apparent benefit was seen in patients 70 years of age or older. Blood clots in this age group were more frequently reported. Your healthcare professional will assess your health and discuss with you whether chemotherapy and PORTRAZZA are an appropriate option for you.

Children and adolescents:

- PORTRAZZA should not be given to patients under the age of 18 years because there is no information about how it works in this age group.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take PORTRAZZA:

- PORTRAZZA is given by intravenous infusion (through a needle placed in a vein in the arm, hand or through a central line). Each infusion lasts approximately 60 minutes.
- PORTRAZZA is given in combination with gemcitabine and cisplatin. You should read the patient information for gemcitabine and cisplatin as well. Your doctor will determine your treatment plan. Ask your doctor or health care team if you have any questions.

Usual dose:

- The recommended dose of PORTRAZZA is 800 mg on days 1 and 8 of each 3-week cycle.
- The number of infusions that you receive will depend on how and for how long you respond to treatment with PORTRAZZA. Your doctor will discuss this with you.

Premedication
- You may be given medicines to reduce the risk of an infusion-related reaction or a skin reaction before you receive PORTRAZZA.
- If you experience an infusion-related reaction during PORTRAZZA therapy, you will be given other medications to reduce or prevent such reactions for all future infusions.
- Symptoms of infusion-related reactions may include increased muscle tension, back pain, chest pain and/or tightness, chills, flushing, difficulty in breathing, wheezing, and feeling of tingling or numbness in hands or feet. In severe cases, symptoms may include breathing distress caused by narrowing of the airways, faster heartbeat, and feeling weak.

Dose Adjustments
- During each infusion, your doctor or nurse will check for side effects. The time over which your infusion is given may lengthen if you experience an infusion-related reaction during treatment.
- Depending on any side effects you have, your treatment may be stopped temporarily and/or permanently.

Overdose

If you think you have received too much PORTRAZZA, contact your healthcare professional, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

Missed Dose
If you miss an infusion, contact your doctor immediately for further instructions.

What are possible side effects from using PORTRAZZA?
Tell your doctor immediately if you experience any of the following serious side effects during PORTRAZZA treatment:
- **Chest pain (may or may not feel like pressure or tightness in your chest) or loss of strength in an arm or leg, change in speech or change in vision** which could be due to blood clots in the arteries (can lead to a heart attack or stroke);
- **Swelling, pain and tenderness in the limb** which can be due to a blood clot in the vein. Blood clots can also develop in the blood vessels of the lung. Symptoms may include difficulty breathing, chest pain, or an abnormal heartbeat and discomfort.
- Low blood levels of magnesium, potassium, calcium or phosphate. Blood samples may be taken before each infusion of PORTRAZZA to measure these electrolyte levels and to determine if supplements are required.

Tell your doctor if you experience any of the following other side effects:

Very common: may affect more than 1 in 10 people
- Skin reactions, such as acne-like rash, itchy dry skin, scaling, skin peeling, nail changes, redness on the palms of hands and feet
- Vomiting
- Fever or high temperature (pyrexia)
- Decreased weight

- Mouth ulcers
- Cold sores

Common: may affect up to 1 in 10 people
- Headache
- Coughing up blood (hemoptysis)
- Nosebleed (epistaxis)
- Strange tastes; metallic taste (dysgeusia)
- Eye reactions, such as inflammation, pink eye, irritation, blurred vision, dry eyes
- Bladder and/or kidney infection (urinary tract infection)
- Pain when passing urine (dysuria)
- Difficulty in swallowing (dysphagia)
- Muscle spasms
- Inflammation of veins in the legs (phlebitis)
- Pain in your mouth and throat (oropharyngeal pain)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Chest pain (may or may not feel like pressure or tightness in your chest) or loss of strength in an arm or leg, change in speech or change in vision which could be due to blood clots in the arteries (can lead to a heart attack or stroke)		✓	
COMMON Swelling, pain and tenderness in the limb which can be due to a blood clot in the vein. Blood clots can also develop in the blood vessels of the lung. Symptoms may include difficulty breathing, chest pain, or an abnormal heartbeat and discomfort		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional. These are not all the possible side effects you may feel when taking PORTRAZZA. If you experience any side effects not listed here, contact your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store PORTRAZZA in a refrigerator at 2 °C – 8 °C (36 °F – 46 °F) until time of use.
- Do not freeze or shake the vial.
- Keep the vial in the outer carton in order to protect from light.
- Keep out of reach and sight of children.

If you want more information about PORTRAZZA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N2E8

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